



Attorney Docket No. P71354US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of SEBILLE et al.

Application No. 10/588,265

Art Unit 1625

Filed August 31, 2006

Examiner Bernard Dentz

For BENZOPYRAN DERIVATIVES, METHOD OF PRODUCTION AND USE THEREOF

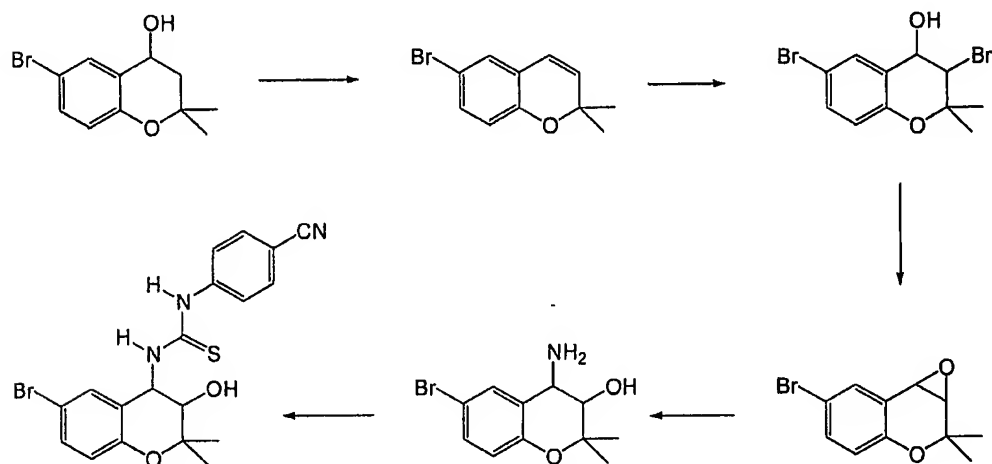
**DECLARATION UNDER 37 CFR 1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

The undersigned Bernard Pirotte and Philippe Lebrun do hereby declare and state:

1. I, Bernard Pirotte, am a citizen of Belgium currently residing in Oupeye, Belgium.
2. I, Philippe Lebrun, am a citizen of Belgium currently residing in Brussels, Belgium.
3. I, Bernard Pirotte, am currently an employee, having the title of Professor, of the Université de Liege, Belgium, an assignee of the subject patent application.
4. I, Philippe Lebrun, am currently an employee, having the title of Professor, of the Université Libre de Bruxelles, Belgium, an assignee of the subject patent application.
5. We are familiar with the rejection of present claims 1-16 under 35 USC 102(b) for allegedly being anticipated by US Pat. No. 5,276,168 (Atwal) in the Office Action mailed February 26, 2008, and submit the instant declaration to address the rejection.
6. Under our direction and control a 3-hydroxy-substituted benzopyran derivative ("Compound B") and its corresponding 3-hydrogeno-substituted benzopyran derivative ("Compound A") were synthesized and the effects of each on insulin secretion from rat pancreatic islets recorded, as follows:

**Synthesis of 3S,4R/3R,4S-6-bromo-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol**



**6-Bromo-2,2-dimethyl-2H-1-benzopyran**

R/S-6-bromo-3,4-dihydro-2H-1-benzopyran-4-ol (7 g, 0.0273 mol) (obtained as described by Khelili et al. *Pharm. Pharmacol. Commun.* 1999, 5, 189-193) and p-toluenesulfonic acid (0.6 g, 0.00349 mol) were dissolved in toluene (100 mL) and then refluxed in a Dean-Stark apparatus during 90 minutes. After elimination of the solvent under reduced pressure, the residue was partitioned between water and ether. The organic layer was washed with a 10% aqueous solution of NaHCO<sub>3</sub>, dried over magnesium sulphate, and then concentrated under reduced pressure. The resulting oil (title compound) was used in the next step without further purification.

**3R,4S/3S,4R-3,6-dibromo-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-ol**

6-Bromo-2,2-dimethyl-2H-1-benzopyran (6 g, 0.02521 mol) was dissolved in DMSO (50 mL) and water (4 mL) and supplemented with N-bromosuccinimide (6 g, 0.03371 mol). The mixture was stirred for 90 minutes at room temperature. The title compound was partitioned between water and ethyl acetate and the organic layer was

washed with water, dried over magnesium sulphate and concentrated under reduced pressure. The resulting oil (title compound) was used in the next step without further purification.

3R,4S/3S,4R-6-bromo-3,4-dihydro-2,2-dimethyl-3,4-epoxychromane

3R,4S/3S,4R-3,6-dibromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (8 g, 0.0239 mol) was dissolved in anhydrous diethyl ether (500 mL) and supplemented with KOH (5 g, 0.2679 mol). The reaction mixture was stirred for 24 h at room temperature and then filtered. The filtrate was concentrated under reduced pressure. The resulting oil (title compound) was used in the next step without further purification.

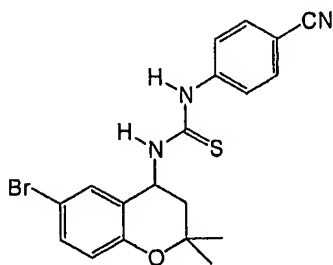
3S,4R/3R,4S-4-amino-6-bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol

3R,4S/3S,4R-6-bromo-3,4-dihydro-2,2-dimethyl-3,4-epoxychromane (5.4 g, 0.02126 mol) was dissolved in ethanol (50 mL) and supplemented with a 25% aqueous solution of ammonia (100 mL). The mixture was stirred for 72 h at room temperature and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was separated, dried over magnesium sulphate and concentrated under reduced pressure. The solid residue was crystallized in ethyl acetate, m.p. 131 °C.

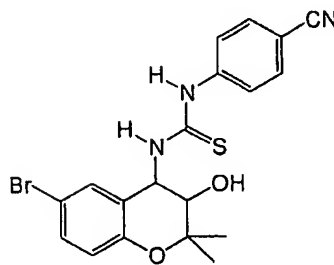
3S,4R/3R,4S-6-bromo-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol

The solution of 3S,4R/3R,4S-4-amino-6-bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol (0.4 g, 0.00189 mol) in dichloromethane (5 mL) was supplemented with 4-cyanophenyl isothiocyanate (1.2 equiv.) and the mixture was stirred for 20 minutes at room temperature. The title compound which precipitated was collected by filtration, washed with petroleum ether 40-60°C and dried, m.p. 126-130°C.

**Effects of the benzopyran derivatives on insulin secretion from rat pancreatic islets**



**Compound A**



**Compound B**

The residual insulin secretion (%) was measured on rat pancreatic islets for the two compounds at 1  $\mu$ M and provided the following results (mean  $\pm$  s.e.m. (n)) :

**Compound A** (example 33: R/S-6-bromo-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzpoyran):  $57.48 \pm 3.00$  % (29)

**Compound B** (3S,4R/3R,4S-6-bromo-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzpoyran-3-ol):  $94.68 \pm 4.84$  % (24)

7. As observed, at 1  $\mu$ M, Compound A provoked a 40% inhibition of the insulin release while Compound B was inactive. Thus, the absence of an OH group at the 3-position surprisingly and unexpectedly results in an improvement of activity on the pancreatic tissue.
8. Comparing the residual insulin secretion for both Compound A and Compound B, Compound B was surprisingly and unexpectedly inactive. The absence of the OH group at the 3-position, therefore, surprisingly and unexpectedly results in an improvement of

activity on the pancreatic tissue. This pancreatic activity is totally different from the cardiovascular, antiischemic, and antiarrhythmic activities disclosed in Atwal.


We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarants sayeth naught

Date July 28 2008

  
Bernard Pirotte

Date July 28 2008

  
Philippe Lebrun

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## **Bernard Pirotte**

### **Curriculum Vitae**

#### Professional address

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#### Private address

5, rue Tollet, B-4680 Oupeye, BELGIUM; Tel: + 32 4 264 04 46

#### Personal information

Date of birth: 10 January 1959

Civil status: Married, 3 children

Citizenship: Belgian

#### Education

- Pharmacist, University of Liège, June 26, 1981

- Doctor's degree: Ph.D. in Pharmaceutical Sciences, University of Liège, February 24, 1989

- "Agréégé de l'Enseignement Supérieur", University of Liège, April 17, 2001

#### Employment

Present status: Professor at the University of Liège

#### Teaching

- Teaching in Medicinal Chemistry, third year Pharmaceutical Sciences Course, University of Liège

- Teaching in Medicinal Chemistry, Masters in Chemical Sciences, University of Liège

- Post-Graduate Teaching in Medicinal Chemistry, University of Liège

- Invited Professor at the University of Lille, France, "Mastère en Drug Design".

#### Professional affiliations

Member of several Societies: *Société Belge des Sciences Pharmaceutiques, Société Royale de Chimie, Société Belge de Physiologie et de Pharmacologie Fondamentales et Cliniques, Société de Chimie Thérapeutique.*

Executive member of the *Bureau de la Division de Chimie Thérapeutique de la Société Royale de Chimie*, affiliated to the European Federation for Medicinal Chemistry.

#### Main research fields in medicinal chemistry

- Synthesis and biological evaluation of new ATP-sensitive potassium channel openers

- Development of pyrido-, thieno- and benzothiadiazine dioxides as positive allosteric modulators of the AMPA receptors

- Development of coumarin derivatives as serine protease inhibitors and anticancer agents

- Pyridinic analogues of nimesulide as putative non steroidal anti-inflammatory drugs

#### Other scientific activities

Associate Editor of *Current Medicinal Chemistry*

Member of the Editorial Advisory Board of *Central Nervous System Agents in Medicinal Chemistry and Medicinal Chemistry Reviews – Online*

Referee of several journals in the field of medicinal chemistry and pharmacology such as *J. Med. Chem., Eur. J. Med. Chem., Bioorg. Med. Chem. Lett., Curr. Med. Chem., Brit. J. Pharmacol., Tetrahedron Lett., Current Topics in Medicinal Chemistry, ChemBioChem, Talanta, ...*

#### Publications and patents

Author or co-author of more than 250 scientific publications

Inventor or co-inventor on 17 patents

## PUBLICATIONS

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- B. PIROTTE  
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- Synthèse de dérivés 3-aminoalkyl-2-aryl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxydes et leur évaluation en tant qu'antagonistes de la cholécystokinine  
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Nouveaux dérivés de benzothiadiazines fluorées, leur procédé de préparation et les compositions pharmaceutiques qui les contiennent  
Brevet Français n° 0400689, 26/01/2004; PCT EP 05290160.0, 25/01/2005

- S. SEBILLE, P. DE TULLIO, S. BOVERIE, M.-H. ANTOINE, P. LEBRUN, B. PIROTTE  
Benzopyran derivatives, method of production and use thereof  
Brevet Européen n° 04075293.3, 03/02/2004;  
PCT/EP2005/050275, 21/01/2005; WO 2005/075463 A1, 18/08/2005

- V. DETRY, S. COUNEROTTE, B. PIROTTE  
Pyrimidinetrione derivatives, their preparation and use  
Brevet Européen n° 04077400.2, 24/08/2004

- B. PIROTTE, S. COUNEROTTE, V. DETRY, F. FRANKENNE, J.-M. FOIDART, A. NOEL  
5-(1,1'-Biphenyl)-4-yl-5-(4-4-aminoacylphenyl)-piperazin-1-yl-pyrimidine-2,4,6-trione derivatives, as inhibitors of zinc metalloproteinases, their preparation and use.  
PCT/EP2005/054035, 16/08/2005; WO 2006/021533 A1

## CURRICULUM VITAE

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Medical Doctor, « Université Libre de Bruxelles » (Belgium), 1979

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### Appointments :

Research Director at the National Fund for Scientific Research (Belgium)

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### Teaching:

Teaching in Pharmacology at the Faculty of Medicine, at the School of Dentistry and at the "Institut des Sciences de la Motricité", "Université Libre de Bruxelles", Belgium.



Research fields:

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Original articles: more than 120 in journals such as Am. J. Physiol., Biochem. Biophys., Res. Commun., Biochem. Pharmacol., Biochim. Biophys. Acta, Biophys. J., Br. J. Pharmacol., Cell Calcium, Diabetes, Diabetologia, Eur. J. Pharmacol., Human Reproduction, J. Med. Chem., J. Pharmacol. Exp. Ther. ....

Reviews & Proceedings of Congress : more than 25

Oral and Poster Communications: more than 200

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Memberships:

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Scientific Awards:

Victor Lange Prize for Diabetes Research, 1983 (Belgium)  
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Zambon Prize, 1987 (Belgium)  
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Activities as reviewer:

Archives Internationales de Pharmacodynamie et de Thérapie  
Biochimica et Biophysica Acta  
British Journal of Pharmacology  
Diabetologia  
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Scientific stay abroad:

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# ORIGINAL ARTICLES

- W.J. Malaisse, A. Sener, A.R. Carpinelli, K. Anjaneyulu, P. Lebrun, A. Herchuelz and J. Christophe.  
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